

Remarks

Entry of the foregoing, reexamination and further and favorable reconsideration of the above-identified application is respectfully requested. By the foregoing amendment, claims 8-15 have been cancelled, without prejudice to the subject matter disclosed therein. No new matter enters by way of this amendment.

Restriction Requirement

The Examiner has maintained the Restriction Requirement first set forth in the Office Action mailed April 21, 2009. Applicants continue to traverse this requirement. The Examiner argues that the claimed methods do not share a substantial structural feature, and further that the medical disorders recited in the claims do not share a common technical features because they purportedly have different known etiologies. Applicants respectfully disagree.

As noted in the May 21, 2009, Response to Restriction Requirement, the claimed methods share a common substantial structural feature: the parallel administration of sodium channel blockers and selective serotonin uptake inhibitors. Furthermore, contrary to the Examiner's statement, the disorders recited in the claimed methods do share a common technical feature – they are all known to be treatable by the administration of sodium channel blockers. Again, by co-administering a sodium channel blocker with a selective serotonin uptake inhibitor, the applicants surprisingly and unexpectedly found that a marked increase in the sodium channel blocking activity is obtained. Thus, applicants have shown that by administering a combination of a sodium channel blocker and a selective serotonin uptake inhibitor to a patient suffering from any of the disorders listed in the claims, each of which are known to be treatable by the administration of a sodium channel blocker alone, the sodium channel blocker is more effective in treating said disorders.

Thus, clearly the claimed subject matter is tied together by a single inventive concept, and restriction of the claimed subject matter is improper. Therefore, applicants again respectfully request that the Examiner withdraw this Restriction Requirement.

Furthermore, with respect to the election of species, the applicants again note that examination must be conducted pursuant to the guidelines set forth at MPEP Sec. 803.02. Therefore, if subject matter directed to the use of lamotrigine as the sodium channel blocker and sertraline as the selective serotonin uptake inhibitor is found to be allowable, the examination of the claims must be broadened to include other sodium channel blockers and selective serotonin uptake inhibitors (including those claimed in withdrawn claims 5, 7, 21 and 23).

Rejection Under 35 U.S.C. § 112, Second Paragraph and 35 U.S.C. § 101

Claims 9-11 and 14 have been rejected under 35 U.S.C. § 112, second paragraph, for being indefinite, and 35 U.S.C. § 101, for being an improper process claim. Claims 9-11 and 14 have been cancelled, without prejudice or disclaimer to the subject matter disclosed therein. Thus, applicants respectfully request withdrawal of these rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 101.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-4, 6, 9-11, 14, 16, 18-20 and 22 have been rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over Fitzgerald et al. (2(3) TECHNIQUES IN REGIONAL ANESTHESIA AND PAIN MANAGEMENT 119-129 (1998)) in view of Waldman et al. (12(4) PROGRESS IN ANESTHESIOLOGY 55-64 (1998)) and further in view of Carson et al. (U.S. Patent No. 6,191,142). For at least each of the reasons set forth below, withdrawal of this rejection under 35 U.S.C. § 103(a) is believed to be in order.

Initially, the claimed invention is directed to pharmaceutical compositions comprising both a sodium channel blocker and a selective serotonin uptake inhibitor and the use of such pharmaceutical compositions for treating epilepsy, diseases involving chronic pain, diseases deriving from disorders and/or injuries of the motor system, drug or alcohol addition, incontinence of faeces and urine, inflammation, itching, intracranial edema, ischemia and/or subsequent damage caused by reperfusion or retinopathy. Each of these diseases and disorders were known to be treatable by the administration of

sodium channel blockers. The applicants unexpectedly found that by administering a serotonin uptake inhibitor simultaneously with a sodium channel blocker, a marked increase in the sodium channel blocking activity was observed, accompanied by fewer side effects. (*See* the Application as Filed at 4).

Fitzgerald et al. reviews the results of numerous studies on the efficacy of anti-depressants, anti-convulsants, and anti-arrhythmics for the treatment of chronic pain. With respect to selective serotonin reuptake inhibitors (such as fluoxetine, paroxetine, sertraline and venlafaxine), Fitzgerald et al. notes that “there is little evidence to support their use in the primary treatment of chronic pain.” (Fitzgerald et al. at 121). Furthermore, Fitzgerald et al. makes no mention of administering an anti-convulsant together with an anti-depressant. In fact, Fitzgerald et al. notes that selective serotonin reuptake inhibitors “have significant drug interactions” and therefore teaches away from their use together with other drugs. (*Id.* at 122). Thus, Fitzgerald et al. does not teach the use of a combination of a selective serotonin reuptake inhibitor and an anti-convulsant, such as a sodium channel blocker, in a pharmaceutical composition or a method of treating chronic pain. Moreover, given Fitzgerald et al.’s statements that there is little or no evidence supporting the use of a serotonin reuptake inhibitor for the treatment of chronic pain, one of skill in the art would not have been motivated by Fitzgerald et al. to use a serotonin reuptake inhibitor in a method for treating chronic pain or a pharmaceutical composition to be used in such a method.

Waldman et al. is also a review article and reviews the causes, diagnosis and treatments for neuropathic pain. Waldman et al. teach that anti-convulsants, including sodium channel blockers such as lamotrigine, can be used to treat patients suffering from neuropathic pain. (Waldman et al. at 58 and 60). While Waldman et al. notes that tricyclic anti-depressants were long known to be useful for treating neuropathic pain, it also notes that “newer anti-depressant compounds of the selective serotonin re-uptake inhibitor class including fluoxetine (Prozac) or paroxetine (Paxil) do not appear to be as efficacious in the treatment of neuropathic pain.” (*Id.* at 60). In fact, in Table 2 on page 59 of Waldman et al. it is noted that selective serotonin reuptake inhibitors have “minimal effect in [the treatment of] neuropathic pain.” (*Id.* at 59). Finally, like Fitzgerald et al., Waldman et al. fails to teach or even suggest the co-administration of a

sodium channel blocker and a selective serotonin reuptake inhibitor to a patient for the treatment of chronic pain. Furthermore, like Fitzgerald et al., Waldman et al. would not have even motivated one to use serotonin uptake inhibitors for treating a patient suffering from chronic pain given the disclosure that they have “minimal effect in neuropathic pain.”

Finally, Carson et al. relates to the use of aroyl aminoacyl pyrroles for the treatment of neuropathic pain. While Carson et al. notes that anti-convulsants, including lamotrigine, were known to be useful for treating neuropathic pain, Carson et al. makes no disclosure of the use of serotonin uptake inhibitors in such a method, let alone the use of combinations of a sodium channel blocker, such as lamotrigine, and a serotonin uptake inhibitor for the treatment of neuropathic pain. Thus, like Fitzgerald et al. and Waldman et al., Carson et al. fails to teach or even suggest the co-administration of a sodium channel blocker and a selective serotonin reuptake inhibitor to a patient for the treatment of chronic pain.

Therefore, none of the references cited by the examiner disclose administering any of the drugs disclosed therein in combination. Even if Fitzgerald et al. or Waldman et al. did suggest combining an anti-convulsant with an anti-depressant, given the disclosures by both Fitzgerald et al. and Waldman et al. that serotonin uptake inhibitors at best had minimal effects on chronic pain, one of skill in the art would not have been motivated to use a serotonin uptake inhibitor in such a combination. In fact, if one of skill in the art were motivated to combine drugs known to be useful for treating chronic pain, one of skill in the art would have used drugs having different mechanisms of action that were known to be highly effective for such a treatment so that the effective amounts of the drugs used in combination would be less than the effective amounts used individually, thus reducing known side effects (such as CNS-related toxicity associated with lamotrigine). Thus, one of skill in the art at most would look towards combining two drugs known to be highly effective for treating chronic pain, but from different classes (and therefore that work by different mechanisms), such as an anti-convulsant and a tricyclic anti-depressant. One of skill in the art would expect that such a combination would be effective for treating chronic pain, but would have fewer side effects due to lower dosages of the compounds being administered.

One of skill in the art, however, would not have been motivated to administer in combination an anti-convulsant and a serotonin uptake inhibitor to a patient for the treatment of chronic pain. In fact, one of skill in the art, given the “minimal” effect a serotonin uptake inhibitor has on chronic pain, would have expected that when administered in combination the amount of a sodium channel blocker needed to be effective for treating chronic pain would be the same as if the sodium channel blocker were administered alone. Therefore, there was no motivation in the prior art to administer the compounds together, as one of skill in the art would have expected that there would be no reduction in side effects, or even an improvement in therapeutic efficacy.

Thus, even taken together, Fitzgerald *et al.*, Waldman *et al.* and Carson *et al.* fail to teach or even suggest a pharmaceutical composition comprising a combination of a sodium channel blocker and a serotonin uptake inhibitor, let alone a method of treating chronic pain by administering to a patient such a pharmaceutical composition. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. For this reason alone, the rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

Even if the Examiner had established a *prima facie* case of obviousness, the surprising and unexpected results obtained by the applicants would overcome such a *prima facie* case. As noted above, nothing in the art cited by the Examiner would suggest administering a sodium channel blocker and a serotonin uptake inhibitor simultaneously to a patient for treating chronic pain.

The applicants, however, unexpectedly found that when a sodium channel blocker is administered simultaneously with a serotonin uptake inhibitor, not only is there an unexpected and marked increase in the sodium channel blocking activity, there is also a reduction in side effects. In fact, the applicants have shown that the therapeutic index of lamotrigine increases by about threefold when administered together with 10 mg/kg of fluoxetine – a much greater increase than any one of skill in the art would have expected from administering a compound that was known to have such a minimal effect on chronic pain together with a sodium channel blocker. Thus, contrary to what one of skill in the art would have expected from such a combination, the claimed combination has a much improved therapeutic index when compared to the therapeutic index of a sodium channel

blocker administered alone. (See the Application as Filed at 4). Therefore, the unexpected properties of the claimed combination overcome any finding of a *prima facie* case of obviousness, even if such a *prima facie* case were established (which, as noted above, one has not been established).

In light of these remarks, withdrawal of this rejection under 35 U.S.C. § 103(a) is in order, and the applicants respectfully request such a withdrawal.

Conclusion

Examination and further and favorable reconsideration of this Application is respectfully requested.

Applicants believe that the present Application is in condition for allowance, and therefore respectfully request the issuance of a Notice of Allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Date: December 7, 2009

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